

We claim:

1. A binding protein comprising an antigen binding domain capable of binding human IL-18, said antigen binding domain comprises at least one CDR comprising an amino acid sequence selected from the group consisting of:

CDR-H1. $X_1-X_2-X_3-X_4-X_5-X_6-X_7$ (SEQ ID NO: 42), wherein;

X_1 is S, N, H, R, or Y;

X_2 is Y, G, R, S, or C;

X_3 is W, G, Y, D, S, V, or I;

X_4 is I, H, W, Y, M, L, or D;

X_5 is G, Y, S, N, or H;

X_6 is W, or is not present; and

X_7 is T, S, G, or is not present;

CDR-H2. $X_1-X_2-X_3-X_4-X_5-X_6-X_7-X_8-X_9-X_{10}-X_{11}-X_{12}-X_{13}-X_{14}-X_{15}-X_{16}-X_{17}$
(SEQ ID NO: 43), wherein;

X_1 is F, Y, H, S, or V;

X_2 is I, or F;

X_3 is Y, S, or W;

X_4 is P, Y, or S;

X_5 is G, S, R, or D;

X_6 is D, or G;

X_7 is S, T, G, or R;

X_8 is E, T, I, or N;

X_9 is T, Y, N, I, K, or H;

X_{10} is R, Y, or S;

X_{11} is Y, N, or S;

X_{12} is S, P, A, or V;

X_{13} is P, S, or D;

X_{14} is T, L, or S;

X_{15} is F, K, or V;

X_{16} is Q, S, or K; and

X_{17} is G, or is not present;

CDR-H3. $X_1-X_2-X_3-X_4-X_5-X_6-X_7-X_8-X_9-X_{10}-X_{11}-X_{12}-X_{13}-X_{14}-X_{15}-X_{16}-X_{17}-X_{18}$
(SEQ ID NO: 44), wherein;

X_1 is V, D, E, S, or C;

X_2 is G, R, D, S, K, L, Y, or A;

X_3 is S, G, Y, or R;
 X_4 is G, S, Y, N, T, or D;
 X_5 is W, S, A, G, Y, or T;
 X_6 is Y, G, S, F, W, or N;
 X_7 is P, S, F, Y, V, G, W, or V;
 X_8 is Y, F, D, P, M, I, or N;
 X_9 is T, W, D, L, Y, E, P, F, or G;
 X_{10} is F, D, Y, H, V, Y, or is not present;
 X_{11} is D, Y, F, L, or is not present;
 X_{12} is I, D, Y, or is not present;
 X_{13} is Y, or is not present;
 X_{14} is Y, or is not present;
 X_{15} is G, or is not present;
 X_{16} is M, or is not present;
 X_{17} is D, or is not present; and
 X_{18} is V, or is not present;

CDR-L1. X_1 - X_2 - X_3 - X_4 - X_5 - X_6 - X_7 - X_8 - X_9 - X_{10} - X_{11} - X_{12} - X_{13} - X_{14} - X_{15} - X_{16} - X_{17}

(SEQ ID NO: 45), wherein;

X_1 is R, or K;
 X_2 is A, G, or S;
 X_3 is S;
 X_4 is E, R, Q, or H;
 X_5 is S, I, T, or N;
 X_6 is I, V, L, or F;
 X_7 is S, G, L, N, or R;
 X_8 is S, G, Y, R, N, H, or D;
 X_9 is N, G, Y, R, or S;
 X_{10} is L, Y, S, or D;
 X_{11} is A, L, N, V, G, or D;
 X_{12} is A, N, E, K, G, or is not present;
 X_{13} is K, T, N, or is not present;
 X_{14} is N, Y, T, or is not present;
 X_{15} is Y, L, or is not present;
 X_{16} is L, C, Y, or is not present; and
 X_{17} is A, D, or is not present;

CDR-L2. X_1 - X_2 - X_3 - X_4 - X_5 - X_6 - X_7 (SEQ ID NO: 46), wherein;

X₁ is T, G, S, W, or E;
 X₂ is A, V, T, I, or L;
 X₃ is S, or F;
 X₄ is T, I, N, S, R, or Y;
 X₅ is R, or L;
 X₆ is A, Q, E, or F; and
 X₇ is T, or S;

and

CDR-L3. X₁-X₂-X₃-X₄-X₅-X₆-X₇-X₈-X₉-X₁₀ (SEQ ID NO: 47), wherein;

X₁ is Q, or M;
 X₂ is Q, H, or Y;
 X₃ is Y, N, G, S, or R;
 X₄ is N, H, Y, D, G, V, L, or I;
 X₅ is N, G, I, Y, S, Q, F, or E;
 X₆ is W, S, T, L, I, or F;
 X₇ is P, L, T, D, or I;
 X₈ is S, L, P, C, W, I, or F;
 X₉ is I, T, S, or is not present; and
 X₁₀ is T, or is not present.

2. The binding protein according to claim 1, wherein said at least one CDR comprises an amino acid sequence selected from the group consisting of:

Residues 31-35 of SEQ ID NO.:6; Residues 50-66 of SEQ ID NO.:6; Residues 99-110 of SEQ ID NO.:6;
 Residues 24-34 of SEQ ID NO.:7; Residues 50-56 of SEQ ID NO.:7; Residues 89-98 of SEQ ID NO.:7;
 Residues 31-37 of SEQ ID NO.:8; Residues 52-67 of SEQ ID NO.:8; Residues 100-110 of SEQ ID NO.:8;
 Residues 24-35 of SEQ ID NO.:9; Residues 21-27 of SEQ ID NO.:9; Residues 90-98 of SEQ ID NO.:9;
 Residues 31-35 of SEQ ID NO.:10; Residues 50-65 of SEQ ID NO.:10; Residues 98-107 of SEQ ID NO.:10;
 Residues 24-34 of SEQ ID NO.:11; Residues 50-56 of SEQ ID NO.:11; Residues 89-97 of SEQ ID NO.:11;
 Residues 31-37 of SEQ ID NO.:12; Residues 52-67 of SEQ ID NO.:12; Residues 100-108 of SEQ ID NO.:12;
 Residues 24-35 of SEQ ID NO.:13; Residues 51-57 of SEQ ID NO.:13; Residues 90-98 of SEQ ID NO.:13;
 Residues 31-35 of SEQ ID NO.:14; Residues 50-66 of SEQ ID NO.:14; Residues 99-111 of SEQ ID NO.:14;
 Residues 24-40 of SEQ ID NO.:15; Residues 56-62 of SEQ ID NO.:15; Residues 95-103 of SEQ ID NO.:15;
 Residues 31-37 of SEQ ID NO.:16; Residues 52-67 of SEQ ID NO.:16; Residues 100-109 of SEQ ID NO.:16;
 Residues 24-35 of SEQ ID NO.:17; Residues 51-57 of SEQ ID NO.:17; Residues 90-98 of SEQ ID NO.:17;
 Residues 31-35 of SEQ ID NO.:18; Residues 20-36 of SEQ ID NO.:18; Residues 99-108 of SEQ ID NO.:18;
 Residues 24-34 of SEQ ID NO.:19; Residues 50-56 of SEQ ID NO.:19; Residues 89-97 of SEQ ID NO.:19;

Residues 31-35 of SEQ ID NO.:20; Residues 52-67 of SEQ ID NO.:20; Residues 100-108 of SEQ ID NO.:20;
 Residues 24-35 of SEQ ID NO.:21; Residues 51-57 of SEQ ID NO.:21; Residues 90-98 of SEQ ID NO.:21;
 Residues 31-35 of SEQ ID NO.:22; Residues 50-66 of SEQ ID NO.:22; Residues 99-116 of SEQ ID NO.:22;
 Residues 24-39 of SEQ ID NO.:23; Residues 55-61 of SEQ ID NO.:23; Residues 94-102 of SEQ ID NO.:23;
 Residues 31-37 of SEQ ID NO.:24; Residues 52-67 of SEQ ID NO.:24; Residues 100-109 of SEQ ID NO.:24;
 Residues 24-35 of SEQ ID NO.:25; Residues 51-57 of SEQ ID NO.:25; Residues 90-98 of SEQ ID NO.:25;
 Residues 31-37 of SEQ ID NO.:26; Residues 52-67 of SEQ ID NO.:26; Residues 100-109 of SEQ ID NO.:26;
 Residues 24-35 of SEQ ID NO.:27; Residues 51-57 of SEQ ID NO.:27; Residues 90-98 of SEQ ID NO.:27;
 Residues 31-37 of SEQ ID NO.:28; Residues 52-67 of SEQ ID NO.:28; Residues 100-108 of SEQ ID NO.:28;
 Residues 24-35 of SEQ ID NO.:29; Residues 51-57 of SEQ ID NO.:29; Residues 90-98 of SEQ ID NO.:29;
 Residues 31-37 of SEQ ID NO.:30; Residues 52-67 of SEQ ID NO.:30; Residues 99-109 of SEQ ID NO.:30;
 Residues 24-35 of SEQ ID NO.:31; Residues 51-57 of SEQ ID NO.:31; Residues 90-98 of SEQ ID NO.:31;
 Residues 31-37 of SEQ ID NO.:32; Residues 52-67 of SEQ ID NO.:32; Residues 100-109 of SEQ ID NO.:32;
 Residues 24-35 of SEQ ID NO.:33; Residues 51-57 of SEQ ID NO.:33; Residues 90-98 of SEQ ID NO.:33;
 Residues 31-37 of SEQ ID NO.:34; Residues 52-67 of SEQ ID NO.:34; Residues 100-108 of SEQ ID NO.:34;
 Residues 24-35 of SEQ ID NO.:35; Residues 51-57 of SEQ ID NO.:35; Residues 90-98 of SEQ ID NO.:35;
 Residues 31-35 of SEQ ID NO.:36; Residues 50-66 of SEQ ID NO.:36; Residues 99-116 of SEQ ID NO.:36;
 Residues 24-39 of SEQ ID NO.:37; Residues 55-61 of SEQ ID NO.:37; Residues 94-102 of SEQ ID NO.:37;
 Residues 31-35 of SEQ ID NO.:38; Residues 50-66 of SEQ ID NO.:38; Residues 99-108 of SEQ ID NO.:38;
 Residues 24-35 of SEQ ID NO.:39; Residues 51-57 of SEQ ID NO.:39; Residues 90-98 of SEQ ID NO.:39;
 Residues 31-37 of SEQ ID NO.:40; Residues 52-67 of SEQ ID NO.:40; Residues 97-109 of SEQ ID NO.:40;
 Residues 24-40 of SEQ ID NO.:41; Residues 56-62 of SEQ ID NO.:41; Residues 95-103 of SEQ ID NO.:41.

3. The binding protein according to claim 2, wherein said binding protein comprises at least 3 CDRs.
4. The binding protein according to claim 2 wherein said antigen binding domain comprises a V_H .
5. The binding protein according to claim 4 wherein said V_H comprises an amino acid sequence selected from the group consisting of:
 SEQ ID NO: 6; SEQ ID NO: 8; SEQ ID NO: 10; SEQ ID NO: 12; SEQ ID NO: 14;
 SEQ ID NO: 16; SEQ ID NO: 18; SEQ ID NO: 20; SEQ ID NO: 22; SEQ ID NO: 24;
 SEQ ID NO: 26; SEQ ID NO: 28; SEQ ID NO: 30; SEQ ID NO: 32; SEQ ID NO: 34;
 SEQ ID NO: 36; SEQ ID NO: 38; and SEQ ID NO: 40.

6. The binding protein according to claim 2 wherein said antigen binding domain comprises a V_L .
7. The binding protein according to claim 6 wherein said V_L comprises an amino acid sequence selected from the group consisting of:
SEQ ID NO: 7; SEQ ID NO: 9; SEQ ID NO: 11; SEQ ID NO: 13; SEQ ID NO: 15;
SEQ ID NO: 17; SEQ ID NO: 19; SEQ ID NO: 21; SEQ ID NO: 23; SEQ ID NO: 25;
SEQ ID NO: 27; SEQ ID NO: 29; SEQ ID NO: 31; SEQ ID NO: 33; SEQ ID NO: 35;
SEQ ID NO: 37; SEQ ID NO: 39; and SEQ ID NO: 41.
8. The binding protein according to claim 2 wherein said antigen binding domain comprises a V_H and a V_L .
9. The binding protein according to claim 7 further comprising a V_H wherein said V_H comprises an amino acid sequence selected from the group consisting of:
SEQ ID NO: 6; SEQ ID NO: 8; SEQ ID NO: 10; SEQ ID NO: 12; SEQ ID NO: 14;
SEQ ID NO: 16; SEQ ID NO: 18; SEQ ID NO: 20; SEQ ID NO: 22; SEQ ID NO: 24;
SEQ ID NO: 26; SEQ ID NO: 28; SEQ ID NO: 30; SEQ ID NO: 32; SEQ ID NO: 34;
SEQ ID NO: 36; SEQ ID NO: 38; and SEQ ID NO: 40.
10. The binding protein according to claim 8 wherein said V_L comprises an amino acid sequence of SEQ ID NO: 7, and said V_H comprises an amino acid sequence of SEQ ID NO: 6.
11. The binding protein according to claim 2, further comprising a heavy chain immunoglobulin constant domain selected from the group consisting of: a human IgM constant domain; a human IgG1 constant domain; a human IgG2 constant domain; a human IgG3 constant domain; a human IgG4 constant domain; a human IgE constant domain and a human IgA constant domain.
12. The binding protein according to claim 11 wherein said heavy chain immunoglobulin constant region domain is a human IgG1 constant domain.

13. The binding protein according to claim 12 wherein said human IgG1 constant domain comprises amino acid sequence selected from the group consisting of: SEQ ID NO.:2, and SEQ ID NO.:3.
14. The binding protein according to claim 2, further comprising a light chain immunoglobulin constant domain selected from the group consisting of: a human Ig kappa constant domain; and a human Ig lambda constant domain.
15. The binding protein according to claim 14 wherein said light chain immunoglobulin constant region domain is a human Ig kappa constant domain comprising amino acid sequence SEQ ID NO.:4.
16. The binding protein according to claim 14 wherein said light chain immunoglobulin constant region domain is a human Ig lambda constant domain comprising amino acid sequence SEQ ID NO.:5.
17. The binding protein according to claim 2 wherein said binding protein is selected from the group consisting of: an immunoglobulin molecule; an scFv; a monoclonal antibody; a human antibody; a chimeric antibody; a humanized antibody; a single domain antibody; a Fab fragment; an Fab' fragment; an F(ab')₂; an Fv; and a disulfide linked Fv.
18. The binding protein according to claim 17 wherein said binding protein is a human antibody.
19. A binding protein capable of binding human IL-18, said binding protein comprising:
an Ig constant heavy region having an amino acid sequence selected from the group consisting of: SEQ ID NO:2, and SEQ ID NO: 3;
an IG constant light region having an amino acid sequence selected from the group consisting of: SEQ ID NO:4, and SEQ ID NO: 5;
an Ig variable heavy region having an amino acid sequence of SEQ ID NO:6; and
an Ig variable light region having an amino acid sequence of SEQ ID NO:7.
20. A binding protein capable of binding human IL-18, said binding protein comprising:
an Ig constant heavy region having an amino acid sequence of SEQ ID NO: 3;

- an IG constant light region having an amino acid sequence of SEQ ID NO:4;
 an Ig variable heavy region having an amino acid sequence of SEQ ID NO:6; and
 an Ig variable light region having an amino acid sequence of SEQ ID NO:7.
21. A neutralizing binding protein, wherein said neutralizing binding protein comprises a binding protein according to any one of claims 1-20, and wherein said neutralizing binding protein is capable of neutralizing IL-18.
 22. The neutralizing binding protein according to claim 21 wherein said IL-18 is selected from the group consisting of pro-human IL-18; mature-human IL-18 and truncated-human IL-18.
 23. The neutralizing binding protein according to claim 21 wherein said neutralizing binding protein diminishes the ability of IL-18 to bind to its receptor.
 24. The neutralizing binding protein according to claim 23 wherein said neutralizing binding protein diminishes the ability of pro-human IL-18, mature-human IL-18, or truncated-human IL-18 to bind to its receptor.
 25. The neutralizing binding protein according to claim 21 wherein said neutralizing binding protein is capable of reducing one or more of IL-18 biological activities selected from the group consisting of: Th1 modulation; Th2 modulation; Nk modulation; neutrophil modulation; monocyte-macrophage lineage modulation; neutrophil modulation; eosinophil modulation; B-cells modulation; cytokine modulation; chemokine modulation; adhesion molecule modulation; and cell recruitment modulation.
 26. The neutralizing binding protein according to claim 21, wherein said neutralizing binding protein has a dissociation constant (K_D) selected from the group consisting of: at most about 10^{-7} M; at most about 10^{-8} M; at most about 10^{-9} M; at most about 10^{-10} M; at most about 10^{-11} M; at most about 10^{-12} M; and at most 10^{-13} M.

27. The neutralizing binding protein according to claim 21, wherein said neutralizing binding protein has an on rate selected from the group consisting of: at least about $10^2 \text{M}^{-1} \text{s}^{-1}$; at least about $10^3 \text{M}^{-1} \text{s}^{-1}$; at least about $10^4 \text{M}^{-1} \text{s}^{-1}$; at least about $10^5 \text{M}^{-1} \text{s}^{-1}$; and at least about $10^6 \text{M}^{-1} \text{s}^{-1}$.
28. The neutralizing binding protein according to claim 21, wherein said neutralizing binding protein has an off rate selected from the group consisting of: at most about 10^{-3}s^{-1} ; at most about 10^{-4}s^{-1} ; at most about 10^{-5}s^{-1} ; and at most about 10^{-6}s^{-1} .
29. A labeled binding protein comprising a binding protein of any one of claims 1-20, wherein said binding protein is conjugated to a detectable label.
30. The labeled binding protein of claim 29, wherein the detectable label is selected from the group consisting of a radiolabel, an enzyme, a fluorescent label, a luminescent label, a bioluminescent label, a magnetic label, and biotin.
31. The labeled binding protein of claim 30, wherein said label is a radiolabel selected from the group consisting of: ^3H , ^{14}C , ^{35}S , ^{90}Y , $^{99\text{m}}\text{Tc}$, ^{111}In , ^{125}I , ^{131}I , ^{177}Lu , ^{166}Ho , and ^{153}Sm .
32. A conjugate binding protein comprising a binding protein of any one of claims 1-20, wherein said binding protein is conjugated to a therapeutic or cytotoxic agent.
33. The conjugate binding protein of claim 32, wherein said therapeutic or cytotoxic agent is selected from the group consisting of; an anti-metabolite, an alkylating agent, an antibiotic, a growth factor, a cytokine, an anti-angiogenic agent, an anti-mitotic agent, an anthracycline, toxin, and an apoptotic agent.
34. An isolated nucleic acid encoding a binding protein amino acid sequence of any one of claims 1-20.
35. A vector comprising an isolated nucleic acid according to claim 34.

36. The vector of claim 35 wherein said vector is selected from the group consisting of; pcDNA, pTT, pTT3, pEFBOS, pBV, pJV, and pBJ.
37. A host cell comprising a vector according to any one of claims 35 or 36.
38. The host cell according to claim 37, wherein said host cell is a prokaryotic cell.
39. The host cell according to claim 38, wherein said host cell is E.Coli.
40. The host cell according to claim 37, wherein said host cell is an eukaryotic cell.
41. The host cell according to claim 40, wherein said eukaryotic cell is selected from the group consisting of protist cell, animal cell, plant cell and fungal cell.
42. The host cell according to claim 41, wherein said eukaryotic cell is an animal cell selected from the group consisting of; a mammalian cell, an avian cell, and an insect cell.
43. The host cell according to claim 42, wherein said animal cell is a CHO cell.
44. The host cell according to claim 42, wherein said host cell is COS.
45. The host cell according to claim 41, wherein said eukaryotic cell is *Saccharomyces cerevisiae*.
46. The host cell according to claim 42, wherein said animal cell is an insect Sf9 cell.
47. A method of producing a binding protein that binds human IL-18, comprising culturing the host cell of any one of claims 37-46 in a culture medium under conditions sufficient to produce a binding protein that binds human IL-18.
48. A binding protein produced according to the method of claim 47.

49. A crystallized binding protein comprising a binding protein according to any one of claims 1-28, wherein said binding protein exists as a crystal.
50. The crystallized binding protein according to claim 49, wherein said crystal is a carrier- free pharmaceutical controlled release crystal.
51. The crystallized binding protein according to claim 49, wherein said binding protein has a greater half life in vivo than the soluble counterpart of said binding protein.
52. The crystallized binding protein according to claim 49, wherein said binding protein retains biological activity.
53. A composition for the release of a binding protein said composition comprising:
 - (a) a formulation, wherein said formulation comprises a crystallized binding protein, according to any one of claims 49-52, and an ingredient; and
 - (b) at least one polymeric carrier.
54. The composition according to claim 53, wherein said polymeric carrier is a polymer selected from one or more of the group consisting of: poly (acrylic acid), poly (cyanoacrylates), poly (amino acids), poly (anhydrides), poly (depsipeptide), poly (esters), poly (lactic acid), poly (lactic-co-glycolic acid) or PLGA, poly (b-hydroxybutyrate), poly (caprolactone), poly (dioxanone); poly (ethylene glycol), poly ((hydroxypropyl) methacrylamide, poly [(organo)phosphazene], poly (ortho esters), poly (vinyl alcohol), poly (vinylpyrrolidone), maleic anhydride- alkyl vinyl ether copolymers, pluronic polyols, albumin, alginate, cellulose and cellulose derivatives, collagen, fibrin, gelatin, hyaluronic acid, oligosaccharides, glycaminoglycans, sulfated polyeaccharides, blends and copolymers thereof.
55. The composition according to claim 53, wherein said ingredient is selected from the group consisting of albumin, sucrose, trehalose, lactitol, gelatin, hydroxypropyl- β - cyclodextrin, methoxypolyethylene glycol and polyethylene glycol.
56. A method for treating a mammal comprising the step of administering to the mammal an effective amount of the composition according to claim 53.

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58.
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A method for regulating gene expression of a gene of interest comprising the steps of:

- (a) providing an IL-18 modulator; and
- (b) contacting said modulator to a cell

wherein said gene of interest is selected from the group consisting of Genbank Identification numbers;

NM_000389, NM_002198, NM_002163, NM_006144, NM_006515, NM_007185,
 NM_002288, NM_003661, NM_021958, NM_001335, Hs.382006, NM_020125,
 NM_007210, NM_021798, NM_013324, M11313, D88152, NM_001103,
 U37519, NM_000697, J03600, NM_014578, S66793, U47054,
 L19871, M81181, NM_001188, U15460, NM_014417, Z23115,
 NM_001713, U45878, U37546, U72649, U49187, J03507,
 U50360, XM_071866, NM_005623, Z32765, Z11697, XM_071866,
 U51096, M83667, D87469, L07765, U66468, X14830,
 L29217, X15880, NM_001851, M27691, M37435, X13589,
 X16866, X59131, NM_004393, U73328, L19267, U53445,
 X68277, U48807, NM_001950, U87269, M57730, X52541,
 J04076, X63741, L07077, M62831, M60830, U53786,
 NM_001988, NM_000141, M23668, U60062, NM_000141, U49973,
 U89995, U27326, A28102, M25667, L34357, U19523,
 L01406, U03486, X68285, Z18859, D49958, D43772,
 AC000099, M57731, X53800, M91036, D16583, X64877,
 X58431, M16937, NM_014468, X92814, L19314, M26665,
 D10995, L41147, M24283, S81914, J03171, J00219,
 NM_000619, NM_000585, U31628, X04500, M27492, X01057,
 M26062, Y00081, Y00787, Z31695, X06256, X57206,
 U20734, NM_014879, D31762, D42038, NM_005551, NM_014846,
 X06182, NM_005551, X07730, M13955, M57710, S83362,
 NM_002314, NM_005569, U49957, U89922, X14008, U59914,
 D14497, X59727, NM_000429, U43944, X72755, NM_021230,
 NM_005951, X78710, X70991, M32011, S77763, M58603,
 S76638, M69043, U91616, D86425, L13740, U44848,
 U79251, M27288, AF000234, D50640, L20971, L10343,
 U77735, NM_003579, U17034, AB000584, X63131, D11428,

NM_032940, NM_005035, NM_003579, M18255, L01087, D38128,
 Y10375, D15049, M31166, U59877, NM_003579, U64675,
 S57153, NM_002903, NG_000013, X75042, M83221, NM_000537,
 U22314, S59049, U70426, U22377, U38480, L10338,
 M23178, M69203, NM_005409, D79206, NM_005065, NM_004186,
 J03764, NM_006802, D89077, NM_003037, M91463, D82326,
 L05568, U96094, X83301, D21267, L31529, M62800,
 NM_021014, Z35093, NM_005816, L25444, M95787, NM_005421,
 L47345, M57732, NM_003205, M96956, U19878, M92357,
 M59465, X83490, U37518, NM_003294, U19261, U78798,
 S69790, U53476, L15309, U78722, X57809, U79249,
 AB000464, X77744, U79248, AI420129,
 HG2981-HT3127, HG3548-HT3749, HG870-HT870, HG4333-HT4603,
 HG3111-HT3287, HG4593-HT4998, HG961-HT961, HG1877-HT1917,
 HG3115-HT3291, HG4115-HT4385, and HG3925-HT4195.

58. The method according to claim 57 wherein said modulator is an antagonist.
59. The method according to claim 57 wherein said modulator is IL-18.
60. The method according to claim 57 wherein said modulator is selected from the group consisting of a binding protein according to any one of claims 1-28.
61. A pharmaceutical composition comprising the binding protein of any one of claims 1-28, and a pharmaceutically acceptable carrier.
62. The pharmaceutical composition of claim 61 which further comprises at least one additional therapeutic agent for treating a disorder in which IL-18 activity is detrimental.
63. The pharmaceutical composition of claim 62, wherein said additional agent is selected from the group consisting of: angiogenesis inhibitors; kinase inhibitors; co-stimulation molecule blockers; adhesion molecule blockers; anti-cytokine antibody or functional fragment thereof; methotrexate; corticosteroids; cyclosporin; rapamycin; FK506; and non-steroidal anti-inflammatory agents.

64. A method for reducing human IL-18 activity comprising contacting human IL-18 with the binding protein of any one of claims 1-28 such that human IL-18 activity is reduced.
65. A method for reducing human IL-18 activity in a human subject suffering from a disorder in which IL-18 activity is detrimental, comprising administering to the human subject the binding protein of any one of claims 1-28 such that human IL-18 activity in the human subject is reduced.
66. A method for treating a subject for a disease or a disorder in which IL-18 activity is detrimental by administering to the subject the binding protein of any one of claims 1-28 such that treatment is achieved.
67. The method of claim 66, wherein said disorder is selected from the group comprising rheumatoid arthritis, osteoarthritis, juvenile chronic arthritis, Lyme arthritis, psoriatic arthritis, reactive arthritis, and septic arthritis, spondyloarthropathy, systemic lupus erythematosus, Crohn's disease, ulcerative colitis, inflammatory bowel disease, insulin dependent diabetes mellitus, thyroiditis, asthma, allergic diseases, psoriasis, dermatitis scleroderma, graft versus host disease, organ transplant rejection, acute or chronic immune disease associated with organ transplantation, sarcoidosis, atherosclerosis, disseminated intravascular coagulation, Kawasaki's disease, Grave's disease, nephrotic syndrome, chronic fatigue syndrome, Wegener's granulomatosis, Henoch-Schoenlein purpura, microscopic vasculitis of the kidneys, chronic active hepatitis, uveitis, septic shock, toxic shock syndrome, sepsis syndrome, cachexia, infectious diseases, parasitic diseases, acquired immunodeficiency syndrome, acute transverse myelitis, Huntington's chorea, Parkinson's disease, Alzheimer's disease, stroke, primary biliary cirrhosis, hemolytic anemia, malignancies, heart failure, myocardial infarction, Addison's disease, sporadic, polyglandular deficiency type I and polyglandular deficiency type II, Schmidt's syndrome, adult (acute) respiratory distress syndrome, alopecia, alopecia areata, seronegative arthropathy, arthropathy, Reiter's disease, psoriatic arthropathy, ulcerative colitic arthropathy, enteropathic synovitis, chlamydia, yersinia and salmonella associated arthropathy, spondyloarthropathy, atheromatous disease/arteriosclerosis, atopic allergy, autoimmune bullous disease, pemphigus vulgaris, pemphigus foliaceus, pemphigoid, linear IgA disease,

autoimmune haemolytic anaemia, Coombs positive haemolytic anaemia, acquired pernicious anaemia, juvenile pernicious anaemia, myalgic encephalitis/Royal Free Disease, chronic mucocutaneous candidiasis, giant cell arteritis, primary sclerosing hepatitis, cryptogenic autoimmune hepatitis, Acquired Immunodeficiency Disease Syndrome, Acquired Immunodeficiency Related Diseases, Hepatitis B, Hepatitis C, common varied immunodeficiency (common variable hypogammaglobulinaemia), dilated cardiomyopathy, female infertility, ovarian failure, premature ovarian failure, fibrotic lung disease, cryptogenic fibrosing alveolitis, post-inflammatory interstitial lung disease, interstitial pneumonitis, connective tissue disease associated interstitial lung disease, mixed connective tissue disease associated lung disease, systemic sclerosis associated interstitial lung disease, rheumatoid arthritis associated interstitial lung disease, systemic lupus erythematosus associated lung disease, dermatomyositis/polymyositis associated lung disease, Sjögren's disease associated lung disease, ankylosing spondylitis associated lung disease, vasculitic diffuse lung disease, haemosiderosis associated lung disease, drug-induced interstitial lung disease, radiation fibrosis, bronchiolitis obliterans, chronic eosinophilic pneumonia, lymphocytic infiltrative lung disease, postinfectious interstitial lung disease, gouty arthritis, autoimmune hepatitis, type-1 autoimmune hepatitis (classical autoimmune or lupoid hepatitis), type-2 autoimmune hepatitis (anti-LKM antibody hepatitis), autoimmune mediated hypoglycaemia, type B insulin resistance with acanthosis nigricans, hypoparathyroidism, acute immune disease associated with organ transplantation, chronic immune disease associated with organ transplantation, osteoarthritis, primary sclerosing cholangitis, psoriasis type 1, psoriasis type 2, idiopathic leucopaenia, autoimmune neutropaenia, renal disease NOS, glomerulonephritides, microscopic vasculitis of the kidneys, Lyme disease, discoid lupus erythematosus, male infertility idiopathic or NOS, sperm autoimmunity, multiple sclerosis (all subtypes), sympathetic ophthalmia, pulmonary hypertension secondary to connective tissue disease, Goodpasture's syndrome, pulmonary manifestation of polyarteritis nodosa, acute rheumatic fever, rheumatoid spondylitis, Still's disease, systemic sclerosis, Sjögren's syndrome, Takayasu's disease/arteritis, autoimmune thrombocytopaenia, idiopathic thrombocytopaenia, autoimmune thyroid disease, hyperthyroidism, goitrous autoimmune hypothyroidism (Hashimoto's disease), atrophic autoimmune hypothyroidism, primary myxoedema, phacogenic uveitis, primary vasculitis, vitiligo, acute liver disease, chronic liver diseases, alcoholic cirrhosis, alcohol-induced liver injury, choleosatis, idiosyncratic liver disease, Drug-Induced hepatitis, Non-alcoholic Steatohepatitis, allergy

and asthma, group B streptococci (GBS) infection, mental disorders (*e.g.*, depression and schizophrenia), Th2 Type and Th1 Type mediated diseases, acute and chronic pain, and cancer.

68. A method of treating a patient suffering from a disorder in which IL-18 is detrimental comprising the step of administering the binding protein of any one of claims 1-28 before, concurrent, or after the administration of a second agent, wherein the second agent is selected from the group consisting of an antibody, or fragment thereof, capable of binding human IL-12; methotrexate; an antibody, or fragment thereof, capable of binding human TNF; corticosteroids, cyclosporin, rapamycin, FK506, and non-steroidal anti-inflammatory agents.